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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,734	10/01/2003	Kevin H. Gardner	UTSD:1510-1	4912

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 04/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,734	GARDNER ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 22* is/are pending in the application.

4a) Of the above claim(s) *22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Invention I, Claim 21 in their response of March 12, 2006 is acknowledged. The traversal is on the grounds that the methods of both Inventions I and II introduce the same foreign ligand into the same hydrophobic core of the same PAS domain, and the same resultant change in surface binding specificity is detected. This argument is not found to be persuasive for the reasons previously stated. In brief, because the method of Invention I affects and measures the intramolecular binding of HIF2α, while the method of Invention I affects and measures the intermolecular binding of HIF2α, the changes cannot be the same. Therefore, the two methods are different inventions with different results or outcomes.

Applicants' amendment of Claim 21 is acknowledged. Claims 21 and 22 are pending. Claim 22 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claim 21 is herein considered.

Priority

The priority date of the instant invention is taken to be October 1, 2003, the filing date of the instant application.

Abstract

The Abstract filed October 13, 2005 is objected to for being a single, run-on sentence.

Specification-Objections

The specification is objected to for having, on pages 3-4 and 26-27, two versions of the figure legends.

The specification is objected to for having, on pages 28-31, a series of drawings. MPEP § 1.58 states that the specification, including the claims, may contain chemical and mathematical formulae, but shall not contain drawings or flow diagrams. The drawings presented on pages 28-31, disclosing the structure of chemical compounds, should be removed from the specification and presented in the drawings.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claim 21 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of US Application 10/677,733. Although the

conflicting claims are not identical, they are not patentably distinct from each other. Claim 21 herein and Claim 1 of 10/677,733 are both directed to methods for affecting the intramolecular binding of HIF2α by introducing into the PAS B domain hydrophobic core a foreign ligand, wherein the effect on binding is detected by $^{1}H/^{15}N$-HSQC NMR. The claims differ in that Claim 1 of 10/677,733 also recites methods for affecting the intermolecular binding of HIF2α by introducing into the PAS B domain hydrophobic core a foreign ligand, wherein the effect on binding is detected by $^{1}H/^{15}N$-HSQC NMR as well as other NMR techniques. The portion of the specification in 10/677,733 that supports the recited methods includes embodiments that would anticipate Claim 21 herein (pg 3, parg 5; pg 13, parg 4), e.g., methods for affecting the intramolecular binding of HIF2α by introducing into the PAS B domain hydrophobic core a foreign ligand, wherein the effect on binding is detected by $^{1}H/^{15}N$-HSQC NMR, which are also the methods specifically encompassed by Claim 1 of 10/677,733. Claim 21 herein cannot be considered patentably distinct over Claim 1 of 10/677,733 when there are specifically recited embodiments (methods for affecting the intramolecular binding of HIF2α by introducing into the PAS B domain hydrophobic core a foreign ligand, wherein the effect on binding is detected by $^{1}H/^{15}N$-HSQC NMR) that would anticipate Claim 21 herein. Alternatively, Claim 21 herein cannot be considered patentably distinct over Claim 1 of 10/677,733 when there are specifically disclosed embodiments in 10/677,733 that supports Claim 1 of that application and falls within the scope of Claim 21 herein, because it would have been obvious to a skilled artisan to modify the methods of Claim 1 of 10/677,733 by selecting a specifically disclosed embodiment that supports those claims, i.e., methods for affecting the intramolecular binding of HIF2α by introducing into the PAS B domain hydrophobic core a foreign ligand, wherein the effect on

binding is detected by $^{1}H/^{15}N$-HSQC NMR, as disclosed in 10/677,733. One having ordinary skill in the art would have been motivated to do this, because such an embodiment, methods for affecting the intramolecular binding of HIF2α by introducing into the PAS B domain hydrophobic core a foreign ligand, wherein the effect on binding is detected by $^{1}H/^{15}N$-HSQC NMR, is disclosed as being a preferred embodiment within Claim 1 of 10/677,733 of the other application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 21 uses the phrase "wherein the PAS domain is predetermined, prefolded...". As previously explained in the First Action on the Merits mailed July 14, 2005, neither the claims nor the specification define "predetermined" or "prefolded" and a person of ordinary skill in the art would not know the metes and bounds of the recited invention. Therefore, Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for affecting the intramolecular binding of HIF2α by introducing into the PAS B domain hydrophobic core a foreign ligand, wherein the effect on binding is detected by $^{1}H/^{15}N$-HSQC NMR and, wherein the HIF2α the protein used in the example (pg 14, parg 2), does not reasonably provide enablement for methods for affecting the intramolecular binding of any HIF2α comprising any PAS B domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claim 21 is so broad as to encompass methods for affecting the intramolecular binding of any HIF2α by introducing into the PAS B domain a foreign ligand, wherein HIF2α and PAS B domain have any structure. The scope of this claim not commensurate with the enablement

provided by the disclosure with regard to the extremely large number of methods using an extremely large number of HIF2α comprising a large number of PAS B domains as broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired HIF2α and PAS B domain activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the methods using the HIF2α of the example on page 14.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claim 21, which encompasses methods for affecting the intramolecular binding of any HIF2α by introducing into the PAS B domain a foreign ligand, wherein HIF2α and PAS B domain have any structure. The specification does not support the broad scope of Claim 21 because the specification does not establish: (A) the structure of the HIF2α used in the example on page 14 or any other

polypeptide with HIF2α activity and comprising any PAS B domain, that can be used successfully in the recited method; (B) regions of the protein structure which may be modified without effecting the HIF2α or PAS B domain activity; (C) the general tolerance of the HIF2α and PAS B domain activity to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods for affecting the intramolecular binding of all HIF2α proteins comprising any PAS B domains, wherein HIF2α PAS B domain has any structure. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This claim is directed to a genus of methods for affecting and measuring the intramolcular binding of all HIF2α proteins by introducing a foreign ligand into the PAS B

domain hydrophobic core, wherein the HIF2α protein and PAS B domain have any structure. The specification discloses the results from only one representative species/example of said methods but, in fact, does not teach the structure of the HIF2α protein used in said example. Moreover, the specification fails to describe any other representative species of said methods by any identifying characteristics or properties other than the functionality of being a method for affecting the intramolecular binding of an HIF2α by introducing into the PAS B domain hydrophobic core a foreign ligand, wherein the effect on binding is detected by $^{1}H/^{15}N$-HSQC NMR and wherein the HIF2α and PAS B domain have any structure. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995. Vogtherr et al teach an NMR-based method of detecting ligand binding to proteins, wherein binding is detected by $^{1}H/^{15}N$-HSQC NMR (Fig 2), while Amezcua et al specifically teach the use of $^{1}H/^{15}N$-HSQC NMR to detect ligand binding to the PAS domain of PAS kinase (Fig 4). Neither Vogtherr et al nor Amezcua et al teach the use of $^{1}H/^{15}N$-HSQC NMR to detect

binding of a ligand to a HIF2α PAS B domain. Ema et al teach the identification and characterization of HIF2α (HLF therein), which is a hypoxia-sensitive mediator of transcription comprising PAS domains A and B (Fig 1 & 3D). It would have been obvious to a person of ordinary skill in the art to use the method of Vogtherr et al or Amezcua et al to detect binding of compounds to the HIF2α PAS B domain. Motivation to do derives from the following, which would have been known to the skilled artisan. In response to hypoxia, HIF2α regulates transcription via the Arnt DNA binding protein (Ema et al; Table 1 & Fig 3). The aryl hydrocarbon receptor (Ahr) is an anologous PAS protein that regulates transcription in response to organic carcinogens. Like HIF2α, Ahr regulates transcription via the Arnt DNA binding protein (Fukunaga et al, 1995; Table 1). Thus, for each signaling pair of molecules, the HIF2α or Ahr is the "sensor" molecule, while Arnt is the transcriptional activator. Binding of organic carcinogens to Ahr is via Ahr's PAS B domain (Fukunaga et al; pg 29272, parag 2 & Table 1). A person of ordinary skill in the art would believe that, more likely than not, modulators of HIF2α also bind to the HIF2α PAS B domain. In order to identify modulators of the cell's response to hypoxia, one would be motivated to use the method of Vogtherr et al or Amezcua et al to detect binding of compounds to the HIF2α PAS B domain. Motivation to do so derives from the desire to identify activators, inhibitors, and modulators of the cell's response to hypoxia, which would have use in the treatment of cardiovascular diseases. The expectation of success is high, as methods using $^{1}H/^{15}N$-HSQC NMR to detect binding of ligands to proteins, including PAS domains, are known in the art. Therefore, Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995.

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
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SHERIDAN SWOPE, PH.D.
PRIMARY EXAMINER